ORIGINAL RESEARCH

Predictive Ability of Novel Cardiac Biomarkers ST2, Galectin-3, and NT-ProBNP Before Cardiac Surgery

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***Background*—**Current preoperative models use clinical risk factors alone in estimating risk of in-hospital mortality following cardiac surgery. However, novel biomarkers now exist to potentially improve preoperative prediction models. An assessment of Galectin-3, N-terminal pro b-type natriuretic peptide (NT-ProBNP), and soluble ST2 to improve the predictive ability of an existing prediction model of in-hospital mortality may improve our capacity to risk-stratify patients before surgery.

***Methods and Results*—**We measured preoperative biomarkers in the NNECDSG (Northern New England Cardiovascular Disease Study Group), a prospective cohort of 1554 patients undergoing coronary artery bypass graft surgery. Exposures of interest were preoperative levels of galectin-3, NT-ProBNP, and ST2. In-hospital mortality and adverse events occurring after coronary artery bypass graft were the outcomes. After adjustment, NT-ProBNP and ST2 showed a statistically significant association with both their median and third tercile categories with NT-ProBNP odds ratios of 2.89 (95% confidence interval [CI]: 1.04–8.05) and 5.43 (95% CI: 1.21–24.44) and ST2 odds ratios of 3.96 (95% CI: 1.60–9.82) and 3.21 (95% CI: 1.17–8.80), respectively. The model receiver operating characteristic score of the base prediction model (0.80 [95% CI: 0.72–0.89]) varied significantly from the new multi-marker model (0.85 [95% CI: 0.79–0.91]). Compared with the Northern New England (NNE) model alone, the full prediction model with biomarkers NT-proBNP and ST2 shows significant improvement in model classification of in-hospital mortality.

***Conclusions*—**This study demonstrates a significant improvement of preoperative prediction of in-hospital mortality in patients undergoing coronary artery bypass graft and suggests that biomarkers can be used to identify patients at higher risk. **(*J Am Heart Assoc*. 2018;7:e008371. DOI: 10.1161/JAHA.117.008371.)**

Key Words: cardiac biomarkers • cardiac surgery • mortality • outcomes research

Measures to reduce in-hospital mortality after coronary artery bypass graft (CABG) surgery have involved the development of risk prediction models.[1–8] The ability of current models to improve the predictive ability of in-hospital mortality has not been improved by the addition of additional patient and disease characteristics.[9,10] In recent years, new biomarkers with the ability to measure subtle tissue-level injuries have become available. While an effort to improve the predictive ability of an existing model through the addition of 4 preoperative biomarkers [cardiac troponin T, N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, and blood glucose], did not significantly improve the model's ability to predict in-hospital mortality, the consideration of certain other biomarkers may result in a statistically significant improvement in predictive ability.[11,12]

With the use of a base prediction model of mortality, we can assess the ability of certain biomarkers to improve preoperative prediction of in-hospital mortality in patients with CABG. Given NT-proBNP's strong associations with heart failure, mortality attributable to cardiovascular events, and mortality after cardiac surgery, its inclusion in a prediction model of in-hospital mortality may serve to improve the model's predictive ability.[13–16] Galectin-3, a member of the

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Clinical Perspective

What Is New?

- Current preoperative models use clinical risk factors alone in estimating risk of in-hospital mortality following cardiac surgery.

What Are the Clinical Implications?

- The application of novel cardiac biomarkers ST2, N-terminal pro-brain natriuretic peptide, and Galectin-3 may improve the predictive ability of an existing prediction model of in-hospital mortality may improve our capacity to risk-stratify patients before surgery.

lectin family of proteins, and ST2, a biomarker for cardiac stress, have also been found to be strongly associated with heart failure.[17–22] Additionally, Galectin-3 has been found to be associated with increased risk for all-cause mortality in the Framingham Offspring Cohort.[23] ST2 has been shown to be a sensitive biomarker of cardiac stress with statistically significant differences in concentration when stratified by age or sex.[24,25] We hypothesized that the use of these 3 biomarkers will improve the current risk prediction model used by the American College of Cardiology/American Heart Association CABG guidelines.[26–28]

Methods

To ensure the entire research community can benefit from the data generated by our study group, pending third parties rights, our institution will share the data with the outside researchers upon request. We will ensure the protection of patient privacy associated with clinical data through appropriate de-identification and security measures.

Study Design and Setting

This study used data and blood specimens stored from the Northern New England (NNE) Biomarker Study, a regional consortium in Northern New England with experience in risk prediction in CABG surgery, to conduct a prospective cohort analysis.[7,29,30] This study uses a harmonized data set from 8 medical centers in Vermont, New Hampshire, and Maine in the NNECDSG (NNE Cardiovascular Disease Study Group). The NNECDSG is a voluntary, regional collaborative of clinicians, research scientists and hospital administrators dedicated to improving the quality, safety, and effectiveness of care delivered to patients undergoing cardiac surgery. The NNECDSG registry contains data on patient characteristics, procedural indications, clinical variables, and in-hospital outcomes. Data are periodically validated to ensure that all procedures and end points included in the registry have been accurately assessed. The Committee for the Protection of Human Subjects at Dartmouth College (IRB) approved this study for both the prospective cohort with patient consent and the linkage of readmission and mortality events.

Patient, procedural and outcome data were collected from patients undergoing CABG surgery and/or valve surgery at any of the participating hospitals were prospectively enrolled into the NNE Biomarker Study from 2004 to 2007 (N=1690). Those undergoing isolated CABG (n=1421) and CABG

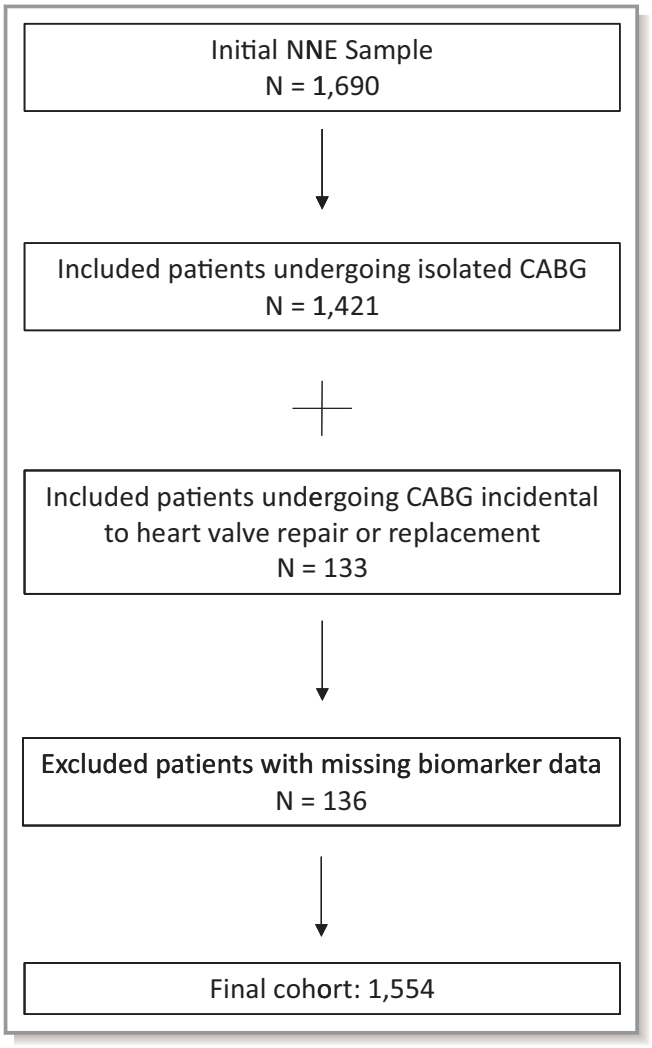

Figure 1. NNE patient cohort flow diagram. Patient, procedural and outcome data were collected from patients undergoing CABG surgery and/or valve surgery at any of the participating hospitals were prospectively enrolled into the NNE Biomarker Study from 2004 to 2007 (N=1690). Those undergoing isolated CABG (n=1421) and CABG incidental to heart valve repair or replacement were included in the analyses (n=133). We excluded patients with missing biomarker data (n=136). The final cohort included 1554 patients. (CABG indicates coronary artery bypass grafting; NNE, Northern New England).

incidental to heart valve repair or replacement were included in the analyses (n=133). Finally, only patients who had all biomarker levels collected were retained in the final analyses (n=1554) (Figure 1). For the present study, the sample included patients undergoing emergent, urgent, and non-urgent CABG surgeries. Collected characteristic and risk factor variables included: patient sex and age, ejection fraction, percentage stenosis of the left main coronary artery, white blood cell count, priority of surgery, prior occurrence of CABG, diabetes mellitus, 3-vessel disease, preoperative renal failure, serum creatinine >2 mg/dL, chronic obstructive pulmonary disease, and vascular disease. Priority of surgery was assessed by cardiothoracic surgeons using previously published definitions.[29]

Sample Collection

Methods for blood sample collection, storage, and analysis have been noted in a prior publication.[11] Blood was collected immediately before induction of isolated CABG at each participating site of the NNECDSG from 2003 to 2007. Blood was allowed to clot at room temperature for 20 minutes to separate out red blood cells before being centrifuged at 1855 g for 20 minutes. The samples were stored at the respective medical centers until transportation to, and analysis at, a central laboratory for preoperative levels of Galectin-3, NT-ProBNP, and ST2.

Primary and Secondary Outcomes

The primary outcome of this study was all-cause in-hospital mortality from the index admission. In-hospital mortality was determined at the time of discharge. Secondary outcomes were new atrial fibrillation, new dialysis, mediastinitis, transient ischemic attack, stroke, low cardiac output, pneumonia, bleeding complications, and leg infection collected prospectively from each medical center.

Statistical Analysis

Differences in risk factors were compared using Pearson's chi-square tests; continuous variables were compared with 2-sample *t* test or Wilcoxon rank-sum tests. Patients were categorized into 2 groups for each biomarker based on the median value of that biomarker. Similarly, patients were equally distributed into terciles for each of the biomarkers. Dummy variables were created for each of the terciles and median values. Logistic regression analysis was used to perform univariate and multivariate analyses assessing the association between these median and tercile categories and the primary and secondary outcomes. The covariate in the multivariate regression models was the predicted score

Table 1. Preoperative Patient Characteristics by Status at Discharge

	Status at Discharge		
	Alive (n=1522)	Deceased (n=32)	*P* Value
Risk factors			
Age	65.2±10.1	70.2±10.7	0.006
Female	351 (23.1%)	15 (46.9%)	0.002
BMI	29.7±5.5	29.0±6.2	0.484
BSA	2.0±0.2	1.9±0.3	0.011
Smoker	345 (22.7%)	7 (21.9%)	0.912
Atrial fibrillation	101 (6.6%)	4 (12.5%)	0.191
CHF	159 (10.5%)	6 (18.8%)	0.132
Preoperative creatinine	1.2±1.0	1.48±1.05	0.066
Diabetes mellitus	570 (37.5%)	11 (34.4%)	0.722
EF <40	159 (11.0%)	6 (11.1%)	0.981
Hypertension	1228 (80.8%)	24 (75.0%)	0.412
Preoperative IABP	58 (3.8%)	5 (15.6%)	0.001
Prior MI			0.819
None	856 (56.2%)	16 (50.0%)	
<24 h preoperative	26 (1.7%)	0 (0.0%)	
>24 h and <7 d	286 (18.8%)	8 (25.0%)	
>7 and <365 d	152 (10.0%)	3 (9.4%)	
>365 d	202 (13.3%)	5 (15.6%)	
VAD	408 (26.8%)	14 (43.8%)	0.033
Unstable angina	829 (55.0%)	25 (80.6%)	0.005
COPD	192 (12.6%)	9 (28.1%)	0.010
Left main stenosis	511 (33.6%)	14 (43.8%)	0.228
Prior CABG	31 (2.1%)	4 (13.3%)	0.000
Prior PCI	300 (19.7%)	7 (21.9%)	0.761
Priority			0.082
Emergency or emergent salvage	29 (1.9%)	1 (3.1%)	
Urgent	1026 (67.4%)	27 (84.4%)	
Non-urgent	467 (30.7%)	4 (12.5%)	
Received transfused blood	565 (37.1%)	27 (84.4%)	0.000
RBCs transfused preoperatively			0.881
0	1489 (98.0%)	32 (100.0%)	
1	9 (0.6%)	0 (0.0%)	
2	15 (1.0%)	0 (0.0%)	
3	7 (0.5%)	0 (0.0%)	

BMI indicates body mass index; BSA, body surface area; CABG; coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; RBC, red blood cell count; VAD, ventricular assist device.

described below. We also conducted multivariate fractional polynomial modeling to further examine associations with biomarker categories and the primary and secondary outcomes. All statistical analyses were performed using the Stata 14.1 statistical program (Stata Corp., College Station, TX).

NNE Base Risk Prediction Model

The NNE base preoperative prediction model of in-hospital mortality in this study was built using preoperative risk scores of risk factors for mortality designated by the American College of Cardiology and American Heart Association.[7,26,31] The in-hospital mortality model corrects for age, sex, ejection fraction <40%, number of diseased vessels, left main disease >50%, white blood cell count, prior myocardial infarction, prior CABG surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease and urgent and emergent priority. The risk scores were used to create a predicted score that served as the one covariate in the logistic models with and without biomarkers to limit over-fitting of the logistic model. New prediction models were built by adding the tercile and median values of Galectin-3, NT-ProBNP, and ST2 to the base model, first by the addition of each individual biomarker and then by adding the panel of 2 biomarkers. The discriminating ability of the regression model was assessed by the c-statistic, which is the area under the receiver operating characteristic (ROC) curve.[32] The cut point for net reclassification improvement (NRI) and integrated discrimination improvement (IDI) calculations is 0.92% for preoperative in-hospital mortality.

Secondary Analyses

As a secondary analyses we applied the well documented 2008 Society of Thoracic Surgeons (STS) CABG risk model to our cohort.[33] We sought to compare risk stratification methods across the models to assess outcomes in the higher risk sub-cohort. The STS CABG risk model includes 35 predictor variables that have been endorsed by an expert panel of cardiothoracic surgeons and biostatisticians.

External Validation Cohort

The TRIBE-AKI (Translational Research Investigating Biomarker End Points for Acute Kidney Injury) study is

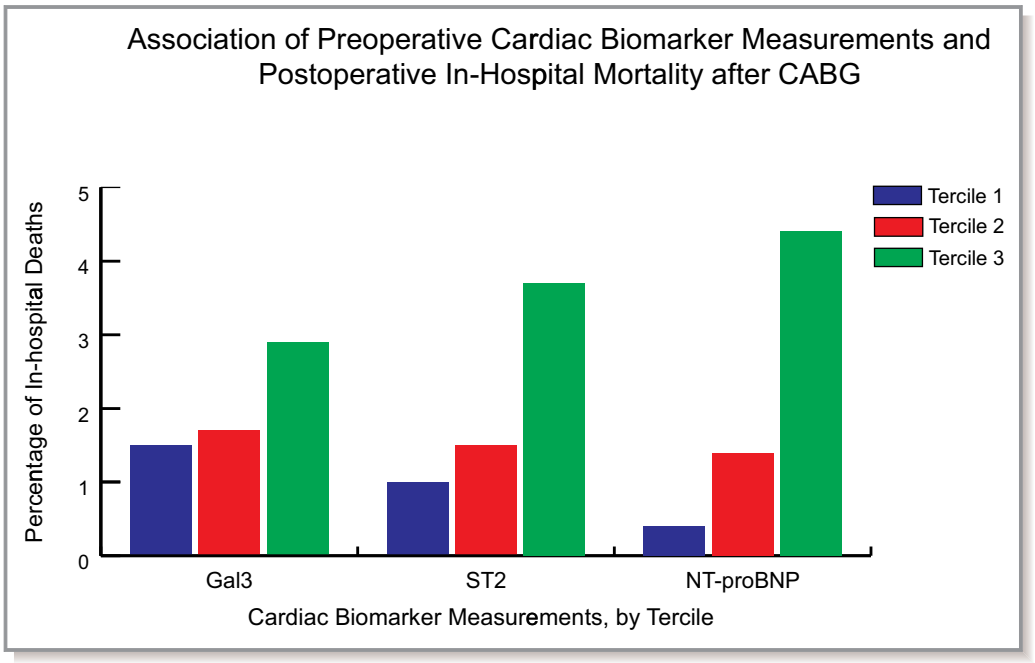

Figure 2. Association of preoperative cardiac biomarker measurements and postoperative in-hospital mortality after CABG. We found a positive association with elevated preoperative novel cardiac biomarkers and in-hospital mortality after CABG surgery. There is a statistically significant association of in-hospital mortality for elevated preoperative ST2 and NT-proBNP tercile levels (P=0.006 and P<0.001, respectively). Preoperative Gal3 terciles yielded a non-significant difference (P=0.250). The addition of ST2 and NT-proBNP to the NNE base risk prediction model significantly improved the preoperative prediction of in-hospital mortality over patient characteristics and risk factors alone. (CABG indicates coronary artery bypass grafting; Gal3, Galectin-3; NNE, Northern New England; NT-proBNP, N-terminal pro b-type natriuretic peptide).

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Table 2. Unadjusted Univariate Associations of Preoperative Biomarker Measurements and Postoperative In-Hospital Outcomes

	Outcomes (OR [95% CI])									
	In-Hospital Mortality	New AFib	New Dialysis	Mediastinitis	Transient Ischemic Attack	Low Cardiac Output	Stroke	Pneumonia	Bleeding Complications	Leg Infection
Gal3										
Median 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Median 2	1.68 (0.82–3.47)	1.44 (1.13–1.84)	1.25 (0.38–4.13)	0.57 (0.19–1.71)	1.77 (0.29–10.64)	1.69 (1.11–2.57)	1.75 (0.83–3.70)	1.59 (0.81–3.13)	1.30 (0.57–2.99)	3.97 (1.10–14.29)
Tercile 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Tercile 2	1.13 (0.43–2.95)	1.35 (0.99–1.84)	0.50 (0.09–2.74)	0.67 (0.19–2.40)	1.11 (0.16–7.94)	1.55 (0.89–2.71)	2.04 (0.82–5.10)	0.58 (0.23–1.48)	0.62 (0.20–1.91)	1.60 (0.27–9.63)
Tercile 3	1.91 (0.80–4.54)	1.54 (1.14–2.09)	1.35 (0.36–5.04)	0.70 (0.20–2.49)	0.65 (0.06–7.17)	2.04 (1.20–3.47)	1.29 (0.48–3.49)	1.44 (0.68–3.04)	1.24 (0.49–3.18)	5.21 (1.12–24.27)
NT-proBNP										
Median 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Median 2	5.53 (2.12–14.44)	1.41 (1.10–1.80)	11.19 (1.43–87.74)	2.83 (0.88–9.07)	0.48 (0.05–4.32)	3.11 (1.95–4.96)	2.84 (1.25–6.41)	1.78 (0.90–3.55)	1.36 (0.59–3.12)	0.84 (0.29–2.42)
Tercile 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Tercile 2	3.52 (0.73–17.04)	1.48 (1.08–2.02)	0.20 (0.04–0.91)	2.08 (0.38–11.41)	0.44 (0.05–4.26)	3.11 (1.45–6.69)	0.57 (0.17–1.96)	1.00 (0.37–2.68)	1.44 (0.54–3.83)	1.07 (0.31–3.74)
Tercile 3	11.89 (2.79–50.73)	1.60 (1.18–2.18)	1 (REF)	4.74 (1.00–22.48)	0.84 (0.09–8.16)	7.66 (3.76–15.59)	2.79 (1.16–6.70)	2.54 (1.11–5.82)	0.91 (0.30–2.72)	0.93 (0.25–3.50)
ST-2										
Median 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Median 2	4.43 (1.81–10.82)	1.12 (0.87–1.42)	2.82 (0.74–10.68)	6.37 (1.42–28.60)	0.84 (0.14–5.09)	1.64 (1.07–2.49)	3.34 (1.43–7.84)	2.30 (1.12–4.71)	0.94 (0.41–2.13)	2.60 (0.81–8.35)
Tercile 1	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Tercile 2	1.60 (0.52–4.93)	1.28 (0.94–1.73)	2.09 (0.19–23.14)	0.71 (0.25–2.08)	0.34 (0.04–3.31)	1.66 (0.95–2.90)	6.58 (1.48–29.32)	2.63 (0.93–7.42)	0.44 (0.13–1.42)	6.09 (0.73–50.83)
Tercile 3	3.88 (1.44–10.48)	1.32 (0.98–1.79)	8.83 (1.10–70.92)	1 (REF)	0.45 (0.05–4.36)	2.14 (1.25–3.66)	7.58 (1.43–7.84)	3.67 (1.35–9.97)	1.15 (0.46–2.85)	7.49 (0.92–61.20)

Model adjusts for age, sex, ejection fraction <40%, presence of any disease, left main stenosis >50%, white blood cell count, prior myocardial infarction, prior coronary artery bypass graft surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease, and urgent and emergent priority. CI indicates confidence interval; Median 1, below median values; Median 2, above median values; New AFib, new atrial fibrillation; OR, odds ratio.

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Table 3. Unadjusted Fractional Polynomials With Preoperative Biomarker Measurements and Postoperative In-Hospital Outcomes

Biomarker Categories	Outcomes (OR [95% CI])									
	In-Hospital Mortality	New AFib	New Dialysis	Mediastinitis	Transient Ischemic Attack	Stroke	Low Cardiac Output	Pneumonia	Bleeding Complications	Leg Infection
Gal3										
Preoperative $Gal3^{0.5}$	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Preoperative $Gal3^{3}$	1.37 (1.02–1.85)	1.16 (1.03–1.30)	1.20 (0.67–2.15)	0.67 (0.19–2.40)	0.83 (0.42–1.66)	1.34 (0.95–1.90)	1.26 (1.05–1.51)	1.27 (0.96–1.69)	1.00 (0.65–1.55)	1.47 (1.10–1.95)
NT-proBNP										
Preoperative BNP^{-2}	0.05 (0.00–0.98)	0.90 (0.83–0.98)	0.00 (0.00–20.59)	0.26 (0.05–1.26)	0.96 (0.84–1.09)	0.83 (0.58–1.18)	0.90 (0.68–1.20)	0.64 (0.35–1.15)	0.93 (0.78–1.10)	0.72 (0.50–1.03)
Preoperative $BNP^{0.5}$	1.24 (1.15–1.35)	1.08 (1.02–1.13)	1.42 (1.24–1.63)	1.23 (1.05–1.44)	1.14 (0.61–2.12)	1.20 (1.11–1.30)	1.22 (1.14–1.31)	1.16 (1.07–1.25)	0.90 (0.74–1.10)	1.09 (0.90–1.33)
ST-2										
Preoperative $ST2^{-1}$	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.98 (0.02–46.42)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Preoperative $ST2^{2}$	0.01 (0.00–0.40)	0.38 (0.16–0.92)	0.00 (0.00–0.30)	0.00 (0.00–0.02)	0.98 (0.94–1.03)	0.01 (0.00–0.11)	0.07 (0.01–0.40)	0.00 (0.00–0.11)	1.79 (0.15–21.65)	0.00 (0.00–0.28)

Model adjusts for age, sex, ejection fraction <40%, presence of any disease, left main stenosis >50%, white blood cell count, prior myocardial infarction, prior coronary artery bypass graft surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease and urgent and emergent priority. CI indicates confidence interval; Gal3, Galectin-3; Median 1, below median values; Median 2, above median values; New AFib, new atrial fibrillation; OR, odds ratio. Superscript values represent fractional powers.

Table 4. NNE Adjusted Multivariate Associations With In-Hospital Mortality

Preoperative Biomarker Category	OR (95% CI)	*P* Value
Galectin-3		
Median 1	1 [REF]	
Median 2	1.08 (0.51–2.29)	0.835
Tercile 1	1 [REF]	
Tercile 2	0.98 (0.36–2.68)	0.971
Tercile 3	1.10 (0.45–2.67)	0.832
NT-ProBNP		
Median 1	1 [REF]	
Median 2	2.89 (1.04–8.05)	0.043
Tercile 1	1 [REF]	
Tercile 2	2.53 (0.51–12.61)	0.258
Tercile 3	5.43 (1.21–24.44)	0.027
ST-2		
Median 1	1 [REF]	
Median 2	3.96 (1.60–9.82)	0.003
Tercile 1	1 [REF]	
Tercile 2	1.81 (0.58–5.65)	0.310
Tercile 3	3.21 (1.17–8.80)	0.023

CI indicates confidence interval; OR, odds ratio.
Model adjusts for age, sex, ejection fraction <40%, presence of any disease, left main stenosis >50%, white blood cell count, prior myocardial infarction, prior coronary artery bypass graft surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease, and urgent and emergent priority.

a prospective cohort of 1417 adults with high risk of acute kidney injury who underwent cardiac surgery (CABG or valve surgery). Participants were prospectively enrolled at 6 academic centers in North America from 2007 through 2010.[34] For Canadian participants, mortality was determined using the Registered Persons Database. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). Full study details were previously described.[34–36]

Short-and Mid-Term Mortality Model Analyses

In addition to postoperative in-hospital mortality, we were interested to evaluate the predictive ability of the NNE and STS models on short-and mid-term mortality with our cohort. We applied the same model parameters already established in the NNE and STS risk models, but focused on 1- and 5-year outcomes.

Results

Descriptive Data

Demographic differences in risk factors and preoperative biomarker levels, after stratification by status at discharge, are presented in Table 1. Of those in our cohort, 32 (2.1%) experienced in-hospital death after surgery. The population of patients who were dead at discharge had a higher proportion of patients who were older (P=0.006), were female (P=0.002), had preoperative intra-aortic balloon pump (P=0.001), had prior CABG (P<0.001), had unstable angina (P=0.005), received blood transfusion (P≤0.001) and COPD (P=0.010). For all 3 biomarkers, the patients who were dead at discharge had much higher, statistically significant, preoperative levels than the patients who were alive.

Univariate Analyses

We found a positive association with elevated preoperative novel cardiac biomarkers and in-hospital mortality after CABG surgery. There was a significant association of in-hospital mortality for elevated preoperative ST2 and NT-proBNP tercile

Table 5. Risk Prediction NNE Models With Added Biomarkers

Biomarker Categories	Prediction Models† (Model ROC [95% CI])						
	NNE Model	NNE+NT-Pro BNP	NNE+ST2	NNE+Gal3	NNE+Gal3+NT-ProBNP	NNE+ST2+NT-ProBNP	NNE+ST2+NT-ProBNP+Gal3
Median	0.80 (0.72–0.89)	0.82 (0.76–0.89)	0.84 (0.76–0.91)	0.80 (0.72–0.89)	0.82 (0.76–0.89)	0.85 (0.79–0.91)	0.85 (0.79–0.91)
P value*	…	0.275	0.128	0.698	0.279	0.048	0.058
Tercile	0.80 (0.72–0.89)	0.83 (0.77–0.90	0.82 (0.74–0.90)	0.80 (0.71–0.89)	0.83 (0.77–0.90)	0.84 (0.78–0.91)	0.84 (0.78–0.91)
P value*	…	0.198	0.352	0.425	0.210	0.072	0.090

CI indicates confidence interval; Gal3, Galectin-3; NNE, Northern New England; NT-ProBNP, N terminal Pro b-type natriuretic peptide.
**P* values compare the area under the ROC curve from the adjusted model to the area under the ROC curve from the base NNE Model.
†Model adjusts for age, sex, ejection fraction <40%, presence of any disease, left main stenosis >50%, white blood cell count, prior myocardial infarction, prior coronary artery bypass graft surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease, and urgent and emergent priority.

Table 6. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the NNE Base Model, at Median and Tercile Cut Points

	Prediction Models†											
	NNE+NT-Pro BNP		NNE+ST2		NNE+Gal3		NNE+Gal3+NT-ProBNP		NNE+ST2+NT-ProBNP		NNE+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.06	0.01	0.02	0.02	0.00	0.00	0.06	0.01	0.13	0.02	0.13	0.02
P value*	0.278	0.001	0.773	0.032	0.398	0.494	0.073	0.001	0.044	0.017	0.045	0.014
Tercile	0.11	0.01	0.03	0.01	0.00	0.00	0.12	0.01	0.10	0.01	0.13	0.02
P value*	0.075	0.022	0.460	0.080	0.505	0.161	0.323	0.023	0.064	0.020	0.039	0.016

IDI indicates integrated discrimination improvement; NNE, Northern New England; NRI, net reclassification improvement.
*The predicted risk threshold based on preoperative biomarkers is 0.92% for NDI and IDI calcuations.
†Model adjusts for age, sex, ejection fraction <40%, presence of any disease, left main stenosis >50%, white blood cell count, prior myocardial infarction, prior coronary artery bypass graft surgery, presence of any vascular disease, presence of diabetes mellitus, history of renal failure, chronic obstructive pulmonary disease and urgent and emergent priority.

levels (P=0.006 and P<0.001, respectively). Preoperative Galectin-3 terciles yielded a non-significant difference (P=0.250) (Figure 2).

Odds ratios resulting from the univariate analysis assessing the relationship between preoperative biomarker are displayed in Tables 2 and 3. The unadjusted univariate analyses found that preoperative NT-ProBNP and ST2 categories were significantly associated with in-hospital mortality. Galectin-3 was associated with new atrial fibrillation, low cardiac output, and leg wound infection morbidities. NT-ProBNP was associated with new atrial fibrillation, new dialysis, stroke, low cardiac output, and pneumonia while ST2 was associated with mediastinitis, new dialysis, stroke, low cardiac output, and pneumonia.

Multivariate Analyses

After adjustment using the predicted score calculated from the risk factors, multivariate regression models using the median and tercile categories of each biomarker are described in Table 4. We found a non-significant association between preoperative Galectin-3 and mortality status at discharge. ST2 and NT-ProBNP median and third tercile measurements had significant associations with in-hospital death, after adjustment for risk factors using the predicted score.

NNE Preoperative Mortality Model

The model ROC score of the base prediction model was 0.80 (95% CI: 0.72–0.89) and is noted in Table 5. The individual addition of each unique biomarker's median and tercile categories to the base model resulted in non-significant improvement in predictive ability of mortality. Applying a fully adjusted model containing median and tercile categories of NT-ProBNP and ST2 biomarkers resulted in an ROC score of 0.85 (95% CI: 0.79–0.91; P=0.048) for the significant difference in the predictive ability for mortality of

Table 7. STS Preoperative Adjusted Multivariate Associations With In-Hospital Mortality

Preoperative Biomarker Category	Odds Ratio (95% CI)	*P* Value
Galectin-3		
Median 1	1 [REF]	
Median 2	1.18 (0.55–2.54)	0.675
Tercile 1	1 [REF]	
Tercile 2	1.06 (0.39–2.91)	0.909
Tercile 3	1.18 (0.47–2.94)	0.728
NT-ProBNP		
Median 1	1 [REF]	
Median 2	2.36 (0.81–6.87)	0.117
Tercile 1	1 [REF]	
Tercile 2	2.23 (0.45–11.12)	0.328
Tercile 3	4.37 (0.93–20.49)	0.061
ST-2		
Median 1	1 [REF]	
Median 2	3.62 (1.43–9.15)	0.007
Tercile 1	1 [REF]	
Tercile 2	1.96 (0.59–6.45)	0.269
Tercile 3	2.96 (1.04–8.41)	0.042

CI indicates confidence interval; NT-ProBNP, N terminal Pro b-type natriuretic peptide.
*Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

Table 8. Risk Prediction STS Models With Added Biomarkers

	Prediction Models† (Model ROC [95% CI])						
	STS Model	STS+NT-Pro BNP	STS+ST2	STS+Gal3	STS+Gal3+NT-ProBNP	STS+ST2+NT-ProBNP	STS+ST2+NT-ProBNP+Gal3
Median	0.86 (0.80–0.92)	0.87 (0.82–0.92)	0.87 (0.81–0.94)	0.86 (0.80–0.92)	0.87 (0.82–0.92)	0.88 (0.83–0.94)	0.88 (0.83–0.94)
P value*	···	0.176	0.301	0.409	0.158	0.048	0.041
Tercile	0.86 (0.80–0.92)	0.88 (0.83–0.93)	0.86 (0.80–0.93)	0.86 (0.80–0.92)	0.88 (0.83–0.93)	0.88 (0.83–0.93)	0.88 (0.83–0.93)
P value*	···	0.136	0.580	0.740	0.135	0.039	0.042

CI indicates confidence interval; Gal3, Galectin-3; NT-ProBNP, N terminal Pro b-type natriuretic peptide; STS, Society of Thoracic Surgeons.
**P* values compare the area under the ROC (receiver operator curve) from the adjusted model to the area under the ROC from the base STS Model.
†Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

this model to the base. With the addition of Galectin-3, a fully adjusted model that contained median categories of all biomarkers (NT-ProBNP, ST2, and Galectin-3) resulted in a shared ROC score of 0.85 (95% CI: 0.79–0.91) and a non-significant *P*-value of 0.058. Compared with the base NNE model alone, the full multi-marker prediction model shows significant improvement in model classification of in hospital mortality. NRI and IDI calculated indices are listed in Table 6.

External Validation Model Performance

We externally validated our results using coefficients from the NNE preoperatively mortality model. The ROC score for the in-hospital clinical model with the TRIBE cohort is 0.67 (95% CI: 0.56–0.78). When we applied the 1-year model using the tercile cut points, the ROC resulted in 0.66 (95% CI: 0.60–0.73). Similarly with the 5-year model the ROC resulted in 0.66 (95% CI: 0.62–0.71).

STS Preoperative Mortality Prediction Model

The model ROC score of the base STS CABG mortality risk prediction was 0.81. STS preoperative adjusted multivariate associations with in-hospital death are described in Table 7. We found few appreciable differences between the predicted risk between the NNE and STS models. Adjusting for the STS model, the NT-proBNP median cut point resulted in less risk and was non-significant (OR 2.36; 95% CI: 0.82–6.87; *P*=0.117) compared with the NNE model (OR: 2.89; 95% CI: 1.04–8.05; *P*=0.043). Similarly, after adjustment, the highest NT-proBNP tercile is associated with 4.37-fold odds of in-hospital death after CABG, but this association is not significant. Risk of in-hospital death, adjusted with the STS model, was significantly higher for preoperative ST2 median and highest tercile cut points; adjustment using the NNE model resulted in similar findings. None of the Galectin-3 results changed meaningfully after adjustment with the STS model.

Table 9. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the STS Base Model, at Median and Tercile Cut Points

	Prediction Models*											
	STS+NT-Pro BNP		STS+ST2		STS+Gal3		STS+Gal3+NT-ProBNP		STS+ST2+NT-ProBNP		STS+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.12	0.00	0.05	0.02	−0.03	0.00	0.12	0.00	0.09	0.02	0.09	0.02
P value*	0.034	0.112	0.276	0.030	0.356	0.574	0.029	0.165	0.008	0.026	0.006	0.031
Tercile	0.10	0.01	0.04	0.01	0.00	0.01	0.10	0.01	0.07	0.02	0.07	0.02
P Value*	0.021	0.098	0.000	0.080	0.590	0.410	0.022	0.094	0.000	0.042	0.000	0.041

CI indicates confidence interval; Gal3, Galectin-3; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-ProBNP, N terminal Pro b-type natriuretic peptide; STS, Society of Thoracic Surgeons.
*Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

Table 10. Risk Prediction Models With Added Biomarkers, Adjusting for the NNE Model, at 1-Year Mortality

	Prediction Models (Model ROC [95% CI])						
	NNE Model	NNE+NT-Pro BNP	NNE+ST2	NNE+Gal3	NNE+Gal3+NT-ProBNP	NNE+ST2+NT-ProBNP	NNE+ST2+NT-ProBNP+Gal3
Median	0.70 (0.64–0.77)	0.73 (0.67–0.78)	0.72 (0.66–0.78)	0.71 (0.64–0.77)	0.73 (0.67–0.79)	0.74 (0.69–0.80)	0.74 (0.69–0.80)
P value*	…	0.183	0.261	0.692	0.159	0.078	0.056
Tercile	0.70 (0.64–0.77)	0.75 (0.70–0.81)	0.71 (0.65–0.78)	0.71 (0.64–0.77)	0.75 (0.70–0.81)	0.76 (0.70–0.81)	0.76 (0.70–0.81)
P Value*	…	0.034	0.444	0.618	0.032	0.031	0.030

CI indicates confidence interval; NNE, Northern New England.
**P* values compare the area under the ROC (receiver operator characteristic) curve from the adjusted model to the area under the ROC curve from the base NNE Model.

C-statistics obtained from models adjusting for the variables in the 2008 STS CABG mortality risk model were higher across the board than those obtained adjusting for the variables in the NNE mortality risk model. The base STS mortality model c-statistic was 0.86 (0.80–0.92) compared with 0.80 (0.72–0.89) for the NNE mortality model alone (Table 8). Adding medians (0.88, CI: 0.83–0.94) and terciles (0.88, CI: 0.83–0.93) of all 3 biomarkers increased the c-statistic relative to the base STS mortality model, and both ROC comparison tests were statistically significant. NRI and IDI calculated indices are listed in Table 9.

Mid-Term Mortality Models

The NNE mortality model had a lower c-statistic when evaluated against 1-year mortality (c-statistic: 0.70, 95% CI: 0.64–0.77), compared with NNE risk prediction of in-hospital mortality at discharge. With the addition of tercile values of ST2 and NT-proBNP, the c-statistic significantly improved to 0.76 (95% CI: 0.70–0.81; *P*=0.031). None of the median cut point values for any of the 3 biomarkers yielded a significant improvement at 1-year mortality after CABG. Table 10 describes these results and Table 11 lists NRI and IDI calculations. When we applied the STS preoperative risk model at 1-year mortality to our NNE cohort, the prediction model yielded a higher c-statistic compared with the NNE mortality model (c-statistic: 0.76 [95% CI: 0.70–0.82]). The addition of ST2 and NT-proBNP tercile values resulted in a statistically significant improvement from the base model to a c-statistic of 0.79 (95% CI: 0.74–0.85; *P*=0.033). When the Galectin-3 tercile values were added to the model, the discriminatory power did not appreciably change (c statistic: 0.80 [95% CI: 0.74–0.85]; *P*=0.032). The STS risk prediction model at 1-year mortality results are listed in Tables 12 and 13.

Tables 14 through 17 describe 5-year mortality prediction from the NNE and STS models. The findings from the NNE clinical mortality model to predict 5-year death was similar to those for 1-year death. The c-statistic from the model alone (0.67; 95% CI: 0.63–0.71) was lower than for one-death or in-hospital death. The additions of preoperative NT-proBNP median (0.72, CI: 0.69–0.75) and tercile values (0.72, CI: 0.69–0.76) produced the highest c-statistics of any individual

Table 11. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the NNE Base Model, at Median and Tercile Cut Points—at 1-Year Mortality

	Prediction Models (Model ROC [95% CI])											
	NNE+NT-Pro BNP		NNE+ST2		NNE+Gal3		NNE+Gal3+NT-ProBNP		NNE+ST2+NT-ProBNP		NNE+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.03	0.01	−0.02	0.01	0.06	0.00	0.02	0.01	0.07	0.01	0.04	0.01
P value*	0.543	0.002	0.597	0.005	0.084	0.165	0.750	0.002	0.204	0.000	0.474	0.000
Tercile	0.11	0.01	0.02	0.01	0.00	0.01	0.05	0.02	0.08	0.02	0.09	0.02
P value*	0.047	0.000	0.640	0.012	0.953	0.012	0.338	0.000	0.178	0.000	0.130	0.000

CI indicates confidence interval; Gal3, Galectin-3; IDI, integrated discrimination improvement; NRI, net reclassification improvement NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC, receiver operator characteristic.
**P* values compare the area under the ROC (receiver operator characteristic) curve from the adjusted model to the area under the ROC curve from the base NNE Model.

Table 12. Risk Prediction Models With Added Biomarkers, Adjusting for the STS Model, at 1-Year Mortality

	Prediction Models† (Model ROC [95% CI])						
	STS Model	STS+NT-Pro BNP	STS+ST2	STS+Gal3	STS+Gal3+NT-ProBNP	STS+ST2+NT-ProBNP	STS+ST2+NT-ProBNP+Gal3
Median	0.76 (0.70–0.82)	0.78 (0.72–0.83)	0.76 (0.70–0.83)	0.77 (0.71–0.83)	0.78 (0.73–0.84)	0.78 (0.72–0.84)	0.78 (0.73–0.84)
P value*	…	0.026	0.583	0.246	0.027	0.127	0.078
Tercile	0.76 (0.70–0.82)	0.80 (0.75–0.85)	0.76 (0.70–0.82)	0.76 (0.71–0.83)	0.80 (0.74–0.85)	0.79 (0.74–0.85)	0.80 (0.74–0.85)
P Value*	…	0.124	0.891	0.567	0.100	0.033	0.032

CI indicates confidence interval; Gal3, Galectin-3; NT-ProBNP, N terminal Pro b-type natriuretic peptide; STS, Society of Thoracic Surgeons.
**P* values compare the area under the ROC (receiver operator characteristic) curve from the adjusted model to the area under the ROC curve from the base STS Model.
†Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

biomarker on this sample; both increases were significant at 95% according to the ROC comparison test. The inclusion of preoperative NT-proBNP and ST2 medians (0.73, CI: 0.70–0.76) and terciles (0.74, CI: 0.70–0.77) together both yielded higher c-statistics than from the base NNE clinical model alone (Tables 14 and 15). The results obtained from using the 2008 STS mortality model to predict 5-year death were similar in all cases to the results obtained using the NNE mortality model (Tables 16 and 17).

Discussion

In this observational study of regional data, we used a prospective cohort to assess the ability of 3 biomarkers (Galectin-3, NT-ProBNP, and ST2) to improve a pre-existing multivariate prediction model of mortality in CABG patients. We discovered that the addition of the 2 biomarkers resulted in a statistically significant improvement in the predictive ability of the model. Simultaneous addition of NT-ProBNP and ST2 into the base prediction model of mortality resulted in a greater ROC score when compared with the base, 0.80 versus 0.85, with a significant *P*-value of 0.048.

Multi-marker risk prediction has been sparsely evaluated for preoperative risk prediction in CABG surgery. Prior work aimed at improving the predictive ability of models of risk of in-hospital mortality after CABG surgery through the addition of 4 biomarkers (cardiac troponin T, NT-ProBNP, high-sensitivity C-reactive protein, and glucose and hemoglobin) to the existing model had found no statistically significant improvement in the model's ability to predict mortality.[11] NT-ProBNP has been shown to predict postoperative survival in patients with aortic stenosis, in-hospital mortality in patients with heart failure, all-cause mortality within 30 days of discharge after non-cardiac surgery, and all-cause mortality in adults with congenital heart disease.[37–40] Preoperative levels of its sister compound, brain natriuretic peptide (BNP), have been used to predict

Table 13. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the STS Base Model, at Median and Tercile Cut Points—at 1-Year Mortality

	Prediction Models* (Model ROC [95% CI])											
	STS+NT-ProBNP		STS+ST2		STS+Gal3		STS+Gal3+NT-ProBNP		STS+ST2+NT-ProBNP		STS+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.09	0.00	0.03	0.01	0.02	0.00	0.12	0.04	0.12	0.03	0.12	0.04
P value*	0.053	0.037	0.218	0.011	0.573	0.437	0.000	0.000	0.001	0.000	0.001	0.000
Tercile	0.11	0.01	0.02	0.01	0.01	0.00	0.11	0.04	0.11	0.04	0.13	0.05
P value*	0.027	0.010	0.418	0.015	0.724	0.063	0.003	0.000	0.001	0.000	0.000	0.000

CI indicates confidence interval; Gal3, Galectin-3; NT-ProBNP, N terminal Pro b-type natriuretic peptide; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC; receiver operator characteristic; STS, Society of Thoracic Surgeons.
*Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

Table 14. Risk Prediction Models With Added Biomarkers, Adjusting for the NNE Model, at 5-Year Mortality

	Prediction Models (Model ROC [95% CI])						
	NNE Model	NNE+NT-Pro BNP	NNE+ST2	NNE+Gal3	NNE+Gal3+NT-ProBNP	NNE+ST2+NT-ProBNP	NNE+ST2+NT-ProBNP+Gal3
Median	0.67 (0.63–0.71)	0.72 (0.69–0.75)	0.70 (0.66–0.74)	0.69 (0.65–0.73)	0.73 (0.69–0.76)	0.73 (0.70–0.76)	0.74 (0.71–0.77)
P value*	…	0.000	0.014	0.063	0.000	0.000	0.000
Tercile	0.67 (0.63–0.71)	0.73 (0.69–0.76)	0.70 (0.67–0.74)	0.70 (0.66–0.73)	0.74 (0.70–0.77)	0.74 (0.70–0.77)	0.74 (0.71–0.78)
P value*	…	0.001	0.013	0.034	0.000	0.000	0.000

CI indicates confidence interval; Gal3, Galectin-3; NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC; receiver operator characteristic.
**P* values compare the area under the ROC (receiver operator characteristic) curve from the adjusted model to the area under the ROC curve from the base NNE (Northern New England) model.

postoperative mortality in patients undergoing cardiac surgery procedures, including CABG.[41,42] Additionally, studies on patients undergoing isolated CABG found associations between preoperative levels of NT-ProBNP and postoperative mortality, prompting inclusion of preoperative levels of the biomarker into our models.[16,43,44]

In regards to the other biomarkers in our multi-marker model, the inclusion of preoperative levels of Galectin-3 in the model was supported given this biomarkers association with health complications and mortality in patients with heart failure.[45,46] Much work has also been conducted to establish associations between ST2 levels and clinical outcomes before and after cardiovascular procedures in specific populations.[47–50] The individual and combined predictive power of these 3 biomarkers, in addition to boost in predictive ability they have provided to existing preoperative models of mortality and risk in many cardiovascular conditions and procedures, merited their congruent consideration in a multi-marker model aimed at preoperatively predicting in-hospital mortality in patients after CABG.[51–53]

Though the sole inclusion of any of the 3 biomarkers into our model individually did not show statistically significant improvement in predictive ability, there was a noticeable increase in the ROC score after the inclusion of ST2 and NT-ProBNP simultaneously. However, though studies that investigated individual biomarkers in our multi-marker model have found Galectin-3 to be significantly associated with heart failure and other cardiovascular outcomes, the results of our univariate and multivariate logistic regression analyses suggest that this association does not extend to in-hospital mortality.

When we compared our model and cohort to the well documented risk prediction methods developed by STS, we observed statistically significant improvement in the discriminating ability with the inclusion of 2 biomarkers compared with the STS clinical base model alone. The addition of median and tercile cut points for NT-proBNP and ST2 yielded a c-statistic of 0.88 versus base model of 0.86. The predictive ability did not change with the addition of Galectin-3. Similar to the NNE risk prediction model findings, the individual inclusion of any of the 3 biomarkers into the STS model did not yield a statistically significant improvement the model.

We were interested to evaluate the predictive ability of our NNE risk models with short and mid-term mortality

Table 15. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the NNE Base Model, at Median and Tercile Cut Points—at 5-Year Mortality

	Prediction Models (Model ROC [95% CI])											
	NNE+NT-Pro BNP		NNE+ST2		NNE+Gal3		NNE+Gal3+NT-ProBNP		NNE+ST2+NT-ProBNP		NNE+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.08	0.03	0.06	0.02	0.05	0.01	0.12	0.04	0.12	0.03	0.12	0.04
P value*	0.042	0.000	0.050	0.000	0.138	0.000	0.000	0.000	0.001	0.000	0.001	0.000
Tercile	0.08	0.03	0.06	0.01	0.07	0.02	0.11	0.04	0.11	0.04	0.13	0.05
P value*	0.021	0.000	0.055	0.000	0.022	0.000	0.003	0.000	0.001	0.000	0.000	0.000

CI indicates confidence interval; Gal3, Galectin-3; IDI, integrated discrimination improvement; NNE; Northern New England; NRI, net reclassification improvement; NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC; receiver operator characteristic.
**P* values compare the area under the ROC (receiver operator characteristic) curve from the adjusted model to the area under the ROC curve from the base NNE (Northern New England) model.

Table 16. Risk Prediction Models With Added Biomarkers, Adjusting for the STS Model, at 5-Year Mortality

	Prediction Models (Model ROC [95% CI])						
	STS Model	STS+NT-Pro BNP	STS+ST2	STS+Gal3	STS+Gal3+NT-ProBNP	STS+ST2+NT-ProBNP	STS+ST2+NT-ProBNP+Gal3
Median	0.69 (0.65–0.73)	0.73 (0.70–0.77)	0.71 (0.67–0.75)	0.71 (0.67–0.75)	0.74 (0.71–0.78)	0.74 (0.70–0.78)	0.75 (0.72–0.79)
P value*	…	0.001	0.021	0.045	0.000	0.000	0.000
Tercile	0.69 (0.65–0.73)	0.74 (0.70–0.77)	0.72 (0.68–0.75)	0.71 (0.68–0.75)	0.75 (0.72–0.78)	0.75 (0.71–0.78)	0.76 (0.72–0.79)
P value*	…	0.001	0.025	0.019	0.000	0.000	0.000

CI indicates confidence interval; Gal3, Galectin-3; NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC; receiver operator characteristic; STS, Society of Thoracic Surgeons.
*Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

after CABG. After applying the NNE preoperative clinical model and STS model to our cohort, we found similar results to the in-hospital mortality model. We observed significant improvement to the prediction models with the inclusion of median and tercile preoperative values from biomarkers ST2 and NT-proBNP. The addition of median and tercile Galectin-3 values, to either the NNE or STS model, did not result in any appreciable difference.

There are limitations to consider. We externally validated our model using a multicenter, mixed cardiovascular disease cohort that includes those undergoing CABG, valve, or CABG and valve surgery who are at high risk of acute kidney injury. The lower validation performance may possibly be attributable to the complexity of the TRIBE-AKI cohort. An improvement to external validation would be to identify a biorepository with a large sample size of isolated CABG patients.

Our NNE cohort includes the limited number of deaths at discharge and potential risk of over-fitting. The cohort under study also consisted of a homogeneous population with race not being considered in the prediction score. Future research should conduct similar analyses using a larger sample size. However, our work suggests that current risk prediction models may be improved by inclusion of biomarkers. Future work should aim to investigate the existence and impact of other biomarkers on mortality after CABG.

CABG is the most common open-heart surgery performed to treat heart disease.[54] Our data are from 2004–2007, when the prevalence of heart disease was slightly higher compared with current data (221.6 versus 168.5 age-adjusted deaths per 100 000 people). While age-adjusted mortality rates have declined in recent years, heart disease remains the leading cause of death in the United States.[54]

Conclusion

In summary, the addition of NT-ProBNP and ST2 to the risk prediction model significantly improved the preoperative prediction of in-hospital mortality over patient characteristics

Table 17. NRI and IDI Indices for Risk Prediction Biomarker Models Compared With the STS Base Model, at Median and Tercile Cut Points—at 5-Year Mortality

	Prediction Models (Model ROC [95% CI])											
	STS+NT-Pro BNP		STS+ST2		STS+Gal3		STS+Gal3+NT-ProBNP		STS+ST2+NT-ProBNP		STS+ST2+NT-ProBNP+Gal3	
Biomarker Categories	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI	NRI	IDI
Median	0.06	0.02	0.04	0.01	0.03	0.01	0.11	0.03	0.10	0.03	0.11	0.04
P value*	0.142	0.000	0.159	0.000	0.224	0.000	0.001	0.000	0.005	0.000	0.002	0.000
Tercile	0.08	0.03	0.03	0.02	0.03	0.02	0.10	0.04	0.07	0.04	0.12	0.05
P value*	0.011	0.000	0.337	0.000	0.291	0.000	0.002	0.000	0.039	0.000	0.001	0.000

CI indicates confidence interval; Gal3, Galectin-3; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-ProBNP, N terminal Pro b-type natriuretic peptide; ROC; receiver operator characteristic; STS, Society of Thoracic Surgeons.
*Model corrects for age, sex, body surface area, atrial fibrillation, last preoperative serum creatinine, presence of diabetes mellitus, ejection fraction <40%, hypertension, preoperative intra-aortic balloon pump use, prior myocardial infarction, presence of any vascular disease, unstable angina, renal failure, chronic obstructive pulmonary disease, left main stenosis >50%, prior coronary artery bypass graft, prior percutaneous coronary intervention, date of operation, and urgent and emergent priority.

and risk factors alone. The use of preoperative biomarkers may have clinical utility in identifying patients at greater risk of mortality after cardiac surgery.

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Disclosures

None.

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